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UNDERSTANDING THE MOLECULAR BASIS OF JN.1

*Dr. Raghavendra Rao M.V[1], Dr.Vijaykumar Chennamchetty[2], Dr. Pavani.G[3], Dr. Manick Dass[4], Dr.Srilatha Basetty[5], Dr Rajkumar Kudari[6], Dr Mahendra Kumar Verma[7], Dr. Abdur Rahman[8], Dr. P. Jaganmohan Rao[9]

[1] Scientist-Emeritus, and Director Research, Apollo Institute of Medical Sciences and Research, Jubilee Hills, Hyderabad, Telangana, India
[2] Associate Professor, Department of Pulmonary Medicine, Apollo Institute of Medical Sciences Education and Research, Hyderabad- (TS)
[3] Department of Clinical Microbiology, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India.
[4] Professor and Head, Department of Clinical Microbiology, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India
[5] Department of Biochemistry, Dr. Patnam Mahender Reddy Institute of Medical Sciences, Chevella, Hyderabad, TS, India.
[6] Professor, Hinducollege of Pharmacy, Guntur, AP, India
[7] Assistant Professor, Basic Medical Sciences, American University School of Medicine, Aruba
[8] Consultant Biochemist, Vijaya Diagnostic center, Tolichowki,Hyderabad, TS, Hyderabad, India
[9] Director, Nuklein Biotec, Haranathapuram, Nellore, AP, India

ABSTRACT

COVID-19 JN.1,subvariant, was initially identified in Luxembourg and is believed to have a connection to the Pirola variant (BA 2.86), which is considered a derivative of the Omicron subvariant. The new Omicron variant of SARS-cov-2 speeding around the world may bring another wave of chaos. It is like walking on a tightrope. The earth is brimming with viruses. The lungs are the paramount respiratory organs. Covid 19 sub variant JN.1 detected in 79 years old Kerala woman. It has been detected in Kerala amid surveillance led by Indian SARS-CoV-2 Genomic Consortium (INSACOG).Originally part of lineage BA.2.86, JN.1 is now recognized as a distinct variant of interest by the WHO. Reassuringly, WHO states that current vaccines remain effective against severe disease and death caused by JN.1 and other circulating COVID-19 variants. In early December, the CDC, reported that the JN.1 subvariant constitutes an estimated 15% to 29% of cases in the United States, as per the agency's most recent projections. According to the CDC, JN.1 was initially identified in the United States in September. Additionally, China reported seven infections of the COVID subvariant.

KEYWORDS: Indian SARS-CoV-2 Genomic Consortium (INSACOG), Pirola variant (BA 2.86)

INTRODUCTION

The SARS-CoV-2 saltation variant BA.2.86, which was quickly designated as a variant under monitoring after its emergence, has garnered global attention.(1,2,3)

This increased binding affinity, could enable BA.2.86 to accumulate immune-evasive mutations, akin to the previous evolution from BA.2.75 to CH.1.1 and XBB.(4,5)

With just one additional receptor binding domain mutation (L455S) compared to its predecessor BA.2.86, the JN.1 variant rapidly became predominant in France, surpassing both BA.2.86 and the so-called FLip (L455F+F456L) strains (6)

The WHO has added a new covid-19 strain, JN.1, to its list of "variants of interest," its second highest level of monitoring.(7)

JN.1 is described by WHO as posing a "low" risk to global public health.(8)

JN.1 was first detected in 12 countries in September, the highest proportions being in Canada, France, Singapore, Sweden, the UK, and the US. (9)

Data from the US Centers for Disease Control and Prevention (CDC) show that JN.1 is the fastest growing covid strain in the US, responsible for 15-29% of new covid infections (10)

It is already the dominant strain in the north east of the US, where it is responsible for a third of all cases (11,12)

Several variants of the virus have been identified, among which five were defined as variants of concern by the World Health Organization: alpha, beta, gamma, delta, and omicron (13)

They may affect disease diagnostics, reduce vaccine mediated

protection from severe illness.(14)

The acute disease caused by SARS-COV-2 is diverse and can range from a mild respiratory disease to a multisystem life threatening syndrome.(15)

Most cases resolve within two to four weeks of the initial symptoms' appearance.(16,17)

The clinical definition of long covid persistent symptoms beyond four weeks from the diagnosis of primary covid-19. (18,19)

It may present with various multi-organ symptoms such as dyspnoea, fatigue, myalgia, cough, cognitive dysfunction, chest pain, and palpitations, which vary in prevalence and severity. (20)

History

JN.1 is closely related to the variant BA.2.86 that CDC has been tracking since August. Even though BA.2.86 and JN.1 sound very different because of the way variants are named, there is only a single change between JN.1 and BA.2.86 in the spike protein. JN.1 was first detected in the United States in September 2023. By the end of October, JN.1 was grouped with BA.2.86 on COVID Data Tracker.

Molecular evolution of SARS-CoV-2

The Omicron variant was sequenced from a viral isolate collected from Gauteng, South Africa in early November 2021. Name of various nSARS-CoV2 variants, their codes, and the countries where they were first detected as listed below; (The variants were named by WHO according to the letter order of the Greek alphabet. The letters Nu and X1 were not used):

U S-Epsilon (B1.249, B1.427 (March 2021) Iota (B 1.526) (March 2021)
Peru (C 37)-(Lambda)
Columbia-August-2021(B1.621 (Mu)
Brazil--(March 2021) (P2) (Zeta) (January 2021) (P.1) (Gamma)
U K (Alpha) (B.1.1.7) (December 2021)
UK and other countries - (Eta) (B.1.525) (March 2021)
South Africa (December-2020) (B.1351) (Beta)
November (B.1.1.529) Omicron (Botswana and other countries)
April 2021) (B.1.6171) (Kappa) (March 2021) (B.1.617.2) (Delta) (India)
Philippines (Theta) (P3) (March 2021)

The Omicron variant of the Covid-19 virus will spread rapidly in India, according to a forecast by Julliet Pulliam, Director of South African DSI-NSF centre for excellence in Epidemiological modeling and analysis. And, told in an interview that it would be wise to prepare for a worst case scenario in terms of hospital planning.

Viral Characteristics

The spike protein of the Omicron variant is characterized by at least 30 amino acid mutations. Notably, 15 of the 30 amino acid substitutions are in the receptor binding domain (RBD). - primary target of vaccine-induced immunity and monoclonal antibody treatment. These mutations are known to lead to increased transmissibility, higher viral binding affinity, and higher antibody escape.

Symptoms

People who are exposed to omicron appear to get sick faster and may have symptoms that are different from those of other variants. In fully vaccinated people and especially after getting the booster, Omicron appears to result in mild illness that can resemble the common cold, (URI –upper respiratory tract infection-Flu-like illness, acute bronchitis-laryngitis), comprises mainly of fever, chills, cough, fatigue or tiredness, congestion, sore throat, hoarse voice and runny nose, typically lasts for ~5 days. (Shortness of breath Pneumonia, hypoxia), loss of taste and smell seems to be quite uncommon).Variants of concern (VOC) are--Alpha, Beta, Gamma and Delta and Omicron

Variants

Delta lineage-B.617.2. Detected first in India,May-21 Transmission increased disease and was also very severe. Omicron lineage-B.1529. Detected first in South Africa,November-21.It is highly transmissible but shows less symptoms. It does not originate from the Delta variant.

Mutations

So many mutations in Omicron. Replication rate of omicron is higher in the bronchus than in lungs as compared to Delta. Omicron leads to less severe disease than other variants.Low viral load inlungs causelesser inflammation in lungs. Mutational land scape of evolved virus renders its high transmissibility. Mutations in the antibody binding site reduces the vaccine effectiveness.

Innate immunity and COVID 19

Innate immunity is the first line of defense against virus invasion. The dendrite cells, macrophages, and neutrophils are the first line of defense and initiate the initial immune reaction upon entry of SARS-CoV-2.Macrophages are the large eaters. These cells show delayed type 1 IFN response.. Natural killer cells are decreased. Exhaustion of NK cells show high expression of NKG2A and low expression of TNF-α, IL-2, CD107 , IFN-γ and decreased cytotoxicity, reduced performance and granzyme secretion The spike glycoproteins (S protein) on the viral envelope binds to its receptor, ACE2, on the surface of human cells to gain entry. This virus entry activates the intracellular pattern recognition receptors (PRRs) that sense the virus associated molecular patterns, such as double-stranded RNA or uncapped mRNA. This triggers the cascade of the cytolytic immune responses, mainly through the type I interferon (IFN) and natural killer cells. Interleukin 6, IL-18 are also released.

Adaptive immunity

The T cells Adaptive immunity plays a major role in the clearance of SARS-CoV-2 from the body and consists of cell mediated immunity and humeral immunity. "T cells can play different roles. They can act as 'killer cells,' attacking cells which have been infected with a virus or another kind

of pathogen, or they can act as 'helper cells' by supporting B cells to produce antibodies." T cells also need the peptides to be bound to specialized cell surface proteins known as MHC molecules. "In vaccinated individuals or those with a prior history of COVID-19, memory T cells will respond quickly if they encounter the same viral peptides bound to the same MHC molecules again. "However, if the peptides they originally recognized are no longer present in the virus as a consequence of mutations, these memory T cells could have lost their purpose. This depends on whether the mutated peptides can still be recognized by them," said Prof. Kern. The Omicron variant of SARS-CoV-2 has many mutations, which scientists believe help it escape neutralizing antibodies. However, if Omicron cannot escape T cells, then they may still have a level of protection against the variant.

Understanding the molecular basis of JN.1

It is known that all the viruses will undergo change, the same is implicated for SARS-CoV-2. However, most of the changes have very Understanding little to no impact on the properties of the virus. The effect may be related to spread or disease severity, efficacy of the vaccines, diagnostic tools, therapeutics, public health and related social measures. With the aim to learn about the variants of SARS-CoV-2, their phenotypes and effects/ complications, the World health organization (WHO) has established a Virus Evolution Working Group, in June 2020. The emerging variants had a very serious impact on public health globally with increasing risk. WHO had characterized the variants as variants of concern (VOCs) and variants of interest (VOIs). This was taken up in the interest to prioritize research for global monitoring, simultaneously to update and adjust the responses of covid-19. WHO began to assign simple and easy to understand labels for the key variants from 2021, May.

The list of currently circulating variants of SARs Cov-2 are:

1. XXB.1.5 its nextstrain clade is 23A. it is a recombinant of BA.2.10.1 and BA.2.75 sublineages- BJ.1 and BM.1.1.1 and has a breakpoint in S1. It has a similar spike genetic profile similar to XBB.1.9.1, rapid risk.
2. XXB.1.16, 23B is the nextstrain clade. Recombinant of BA.210.1 and BA.2.75 sublineages. Initial risk was noted on 17th April 2023.
3. EG.5, no nextstrain is assigned. The genetic features are XBB.1.9.2+S:F456L. initial risk was evaluate on 9th August 2023.
4. BA.2.86$, nextstrain is 23I. It has mutations related to BA.2. Initial risk was evaluated on 21st November 2023.
5. JN.1, no nextstrain code is assigned yet. The genetic features are learnt to be BA.2.86+ S:L455S. Initial risk was evaluated on 18th December 2023.

One of the variants of SARS-CoV2 BA.2.86 was identified on 21st November 2023 and it gathered global attention in no time, has been designated as a Variant of monitoring (VoM). It was learnt to have higher ACE2 (Angiotensin converting enzyme 2) binding affinity coupled with distinct antigenicity further enabling BA.2.86 to accumulate mutations related to immune-evasion, observed at low-level populational transmission. At present JN.1 variant is predominant globally and has just single additional receptor binding domain mutation i.e.L455S when compared to BA.2.86. The mutations noticed are imperative thus, JN.1 surpassed both Flip strains (L455F+ F456L) and BA.2.86 variants. (21,22)

Researchers made an attempt to study the humoral immune evasion of JN.1 variant in two populations, one with vaccination (received 3 doses of inactivated vaccines- Pseudovirus) and had breakthrough infection and the second group included patients reinfected with XBB breakthrough infections related to BA.5 or BF.7. JN.1 is studied to have significantly increased immune escape when compared to BA.2.86. Its plasma evasion exceeded even the competitive variants HV.1 and JD.1.1 and showed significantly low plasma neutralization titres when compared to its parental strains (23).

It has acquired L452R and A475V mutations resulting in reduced binding affinity towards ACE2 (human) led to increased immune evasion compared to XBB.1.5 + HLip (HK.3) and has achieved elevated resistance across the receptor binding domains of Class 1, 2 and 3 antibodies. Due to their antigenic difference such strains may survive and transmit targeting distinct populations when even at low levels. As it has the potential to rapidly assemble high immune-evasion mutations and this is achieved at the cost of the binding capabilities of human ACE2

To summarise JN.1 has acquired a hallmark mutation i.e. S: L455S and 3 mutations in non-S proteins this is contributing towards increased transmissibility and immune escape ability.

The count of variants is dynamic, and as of 2023, the World Health Organization (WHO) recognized nine variants in circulation. Over 50 variants have been identified, though some are no longer actively spreading.

Increased Transmission

Dr Rajesh Karyakarte, genome sequencing coordinator for Maharashtra, says the growth advantage is exponential and cites WHO data that shows how JN.1 rapidly increased from just 3.3 per cent of all coronavirus cases between October 30 and November 5 to 27 per cent a month later. "This is an 86 percent growth advantage,'" says Dr Karyakarte, reasoning that it was due to the increased transmission, immune escape and a prolonged infectious period.(24)

Impact

- The continued growth of JN.1 suggests that it is either more transmissible or better at evading our immune systems. At this time, there is no evidence that JN.1 presents an increased risk to public health relative to other currently circulating variants. There is no indication of increased severity from JN.1 at this time. Updated COVID-19 vaccines are expected to increase protection against JN.1, as they do for other variants. As noted in previous updates, COVID-19 tests and treatments are expected to be effective against JN.1.The rapid growth of JN.1 compared with other variants

raises the question of whether this variant might drive an incremental increase in infections.COVID-19 activity is currently increasing in the United States. We expected this increase because COVID-19 has had a pattern of increasing and peaking in late summer, and then again peaking around the new year. Right now, we do not know to what extent JN.1 may be contributing to these increases or possible increases through the rest of December like those seen in previous years. CDC will closely monitor COVID-19 activity and the spread of JN.1.(25)

New Variant Alert: WHO Flags JN.1 as 'Variant of Interest' with Low Risk

On Tuesday, the World Health Organization (WHO) designated the JN.1 coronavirus strain as a "variant of interest," emphasizing a low risk to public health based on current evidence. Despite its ability to evade the immune system and transmit more quickly than other circulating variants, experts, including virologist Andrew Pekosz from Johns Hopkins Bloomberg School of Public Health, noted no indications of increased disease severity. Originally part of lineage BA.2.86, JN.1 is now recognized as a distinct variant of interest by the WHO. Reassuringly, WHO states that current vaccines remain effective against severe disease and death caused by JN.1 and other circulating COVID-19 variants. In early December, the U.S. Centers for Disease Control and Prevention (CDC) reported that the JN.1 subvariant constitutes an estimated 15% to 29% of cases in the United States, as per the agency's most recent projections. According to the CDC, JN.1 was initially identified in the United States in September. Additionally, last week, China reported seven infections of the COVID subvariant. The CDC assured the public that, at present, there is no evidence indicating that JN.1 poses an increased risk to public health compared to other circulating variants. The CDC suggested that an updated vaccine could protect against this variant.(26)

New Covid variant JN.1 vigil

While sore throat, a runny, stuffy nose, body aches and fever may be symptomatic of most COVID-19 variants, these also show up in influenza and pollution-related upper respiratory chest infection. According to Dr Rommel Tickoo, Director, Internal Medicine, Max Super Speciality Hospital, Saket, New Delhi, there is a high incidence of flu, cough, sore throat and other viral-like illnesses in Delhi NCR attributable to air pollution and colder temperatures. (27)

New COVID variant JN.1: Health Ministry says no need for booster dose

India SARS-CoV-2 Genomics Consortium (INSACOG) chief N.K. Arora speaking to *The Hindu* on December 24 explained that there was no need for an additional fourth booster dose of vaccine against COVID-19 amid the surge in cases and the detection of the JN.1 sub-variant.

Only those over 60 years of age who have comorbidities and high risk patients in this age group can take a precautionary third dose if they have not taken one till now. As of now there is no need for a fourth dose in the general public. We would advise precaution and not panic," said Dr. Arora.(28)

India logs highest number of cases in 225 days, 162 cases of sub-variant JN.1 detected

India logged 797 new cases of Covid-19 and five deaths due to the virus on December 29, the highest in 225 days. Meanwhile, a total of 162 cases of COVID-19 sub-variant JN.1 have been detected in the country, with Kerala reporting the highest number of 83, followed by Gujarat 34, according to the INSACOG's data updated May/19.

A recent study conducted by the Tata Institute for Genetics and Society (TIGS) in Bengaluru has revealed that the JN.1 variant of Covid-19 is the predominant strain found in wastewater samples.

Laboratory Diagnosis

"A number of laboratory-based studies have now shown that the JN.1 variant is less able to infect the lungs as well as other variants and, as a result, is leading to less patients being admitted with pneumonia who require oxygen and *ventilators*.

Two types of tests are used to test for current infection: The gold- standard PCR -nucleic acid amplification tests (NAATs) and Less reliable Rapid antigen tests.

The CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel and the Multiplex Assay for Flu and SARS-CoV-2 are expected to detect the Omicron variant

Changes in the viral genome can result in changes to viral proteins and, therefore, can also impact the performance of an antigen or serology test.

Rapid antigen tests (like Abbott BinaxNOW and Quidel QuickVue antigen tests) can detect the omicron variant.

Timing is critical for rapid tests.

Rapid antigen tests are generally less sensitive and less likely to pick up very early infections (False negative) than PCR-molecular tests for any variant. Since Omicron multiplies so quickly and is so transmissible—and these tests provide only a snapshot in time—you could test negative in the morning and positive by the afternoon.

CONCLUSION

JN.1 90 % minimized a fight for ventilators to a cry for oxygen, the breath of life. It is more contagious and less severe. It causes mild infections like common cold with rapid spread and is an indication for the end of Pandemic. The ultra-contagious omicron mutant is now pushing cases to all-time highs and causing chaos. JN.1 does not yet appear very deadly, but some experts do warm of possible issues like long covid.

REFERENCES

1. Yang S ,Yu Y ,Jian F et al.Antigenicity and infectivity characterisation of SARS-CoV-2 BA.2.86. Lancet Infect Dis.

2023; 23: e457-e459
2. Wannigama DL ,Amarasiri M ,Phattharapornjaroen P ,et al. Tracing the new SARS-CoV-2 variant BA.2.86 in the community through wastewater surveillance in Bangkok, Thailand. Lancet Infect Dis. 2023; 23: e464-e466
3. Wang Q ,Guo Y ,Liu L et al.Antigenicity and receptor affinity of SARS-CoV-2 BA.2.86 spike.Nature. 2023; (published online Oct 23.)https://doi.org/10.1038/s41586-023-06750-w
4. Cao Y ,Song W ,Wang L ,et al. Characterization of the enhanced infectivity and antibody evasion of Omicron BA.2.75.Cell Host Microbe. 2022; 30: 1527-1539
5. Cao Y et al.Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD binding domain evolution.Nature. 2023; 614: 521-529
6. Yue C ,Song W ,Wang L .et al.ACE2 binding and antibody evasion in enhanced transmissibility of XBB.1.5.Lancet Infect Dis. 2023; 23: 278-280
7. Wang Q ,Li Z ,Guo Y ,et al. Evolving antibody evasion and receptor affinity of the Omicron BA.2.75 sublineage of SARS-CoV-2.Science. 2023; 26108254
8. Mahase E Covid-19: New "Pirola" variant BA.2.86 continues to spread in UK and US. BMJ2023;382:p2097. doi:10.1136/bmj.p2097 pmid:37704230
9. Vinall F, Nirappil F. New coronavirus variant JN.1 is spreading fast. Here's what to know. Washington Post 2023 Dec,20. https://www.washingtonpost.com/wellness/2023/12/20/new-covid-variant-jn1-symptoms
10. Roxby P. JN.1 covid variant: WHO charts its rapid global spread. BBC News 2023 Dec 20. https://www.bbc.co.uk/news/health-67772390
11. Roy S. WHO says JN.1 covid strain a "variant of interest," poses low risk. Reuters. 19 Dec 2023. https://www.reuters.com/business/healthcare-pharmaceuticals/who-classifies-jn1-covid-19-variant-interest-2023-12-19/
12. Goodman B. Coronavirus subvariant JN.1 growing fast in US, already dominant in the northeast. CNN Health 2023 Dec 19. https://edition.cnn.com/2023/12/19/health/what-to-know-about-jn-1/index.html
13. Nasserie T, Hittle M, Goodman SN Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review. JAMA Netw Open2021;4:e2111417. doi:10.1001/jamanetworkopen.2021.11417 pmid:34037731
14. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. Nat Med2021;27:601-15. doi:10.1038/s41591-021-01283-z pmid:33753937
15. Ayoubkhani D, Khunti K, Nafilyan V, et al.Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. BMJ2021;372:n693. doi:10.1136/bmj.n693 pmid:33789877
16. Taquet M, Dercon Q, Harrison PJ. Six-month sequelae of post-vaccination SARS-CoV-2 infection: A retrospective cohort study of 10,024 breakthrough infections. Brain Behav Immun2022;103:154-62. doi:10.1016/j.bbi.2022.04.013 pmid:35447302
17. Sivan M, Parkin A, Makower S, Greenwood DC Post-COVID syndrome symptoms, functional disability, and clinical severity phenotypes in hospitalized and nonhospitalized individuals: A cross-sectional evaluation from a community COVID rehabilitation service. J Med Virol2022;94:1419-27. doi:10.1002/jmv.27456 pmid:34783
18. Blomberg B, Cox RJ, Langeland N,Long COVID: A growing problem in need of intervention. Cell Rep Med2022;3:100552. doi:10.1016/j.xcrm.2022.100552 pmid:35474749
19. World Health Organization. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021. https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.
20. Centers for Disease Control and Prevention. Long COVID or Post-COVID Conditions. 2022. https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html
21. Uriu K, Ito J, Kosugi Y, et al. Transmissibility, infectivity, and immune evasion of the SARS-CoV-2 BA.2.86 variant. Lancet Infect Dis 2023; 23(11): e460–e1.
22. Sheward DJ, Yang Y, Westerberg M, et al. Sensitivity of the SARS-CoV-2 BA.2.86 variant to prevailing neutralising antibody responses. Lancet Infect Dis 2023; 23(11): e462–e3.
23. Yamasoba D, Kimura I, Nasser H, et al. Virological characteristics of the SARS-CoV-2 Omicron BA.2 spike. Cell 2022; 185(12): 2103–15.e19
24. Anuradha Mascarenhas,The Indian express,Pune December 22, 2023
25. Update on SARS-CoV-2 Variant JN.1 Being Tracked by CDC,December 8, 2023,
26. Source:https://theprint.in/health/who-says-jn-1-covid-strain-a-variant-of-interest-poses-low-risk/1893262
27. Ankita Upadhyay, The Indian express,Delhhi | December 22, 2023 10:57 IST
28. BINDU SHAJAN PERAPPADAN,The Hindu,December 24, 2023 NEW DELHI